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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/600,521	08/27/2001	Jianyun Dong	22488-710	7109

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EXAMINER	
AKHAVAN, RAMIN	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 05/17/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

5/16/05 LA

Office Action Summary	Application No.	Applicant(s)	
	09/600,521	DONG ET AL.	
	Examiner	Art Unit	
	Ramin (Ray) Akhavan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *16 February 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *47,58,59,61,67-69,71-73 and 115-119* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *47, 58-59, 61, 67-69, 71-73 and 115-119* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Acknowledgment is made of an amendment/response, filed 02/16/2005, canceling claims 60, 66, 70 and 113-114, and amending claims 47, 67 and 71-72. All objections/rejections not repeated herein are hereby withdrawn. Where applicable, a response to Applicant's arguments will be set forth immediately following the body of any objections/rejections set forth herein. Claims 47, 58-59, 61, 67-69, 71-73 and 115-119 are under consideration in this action. As no new grounds of rejection are set forth, **this action is made FINAL.**

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. **Claims 118 and 119 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement.**

This rejection was made in the previous action and is repeated herein. A response to Applicant's arguments is set forth immediately following the body of this rejection. The claims contain subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. More specifically, claims 118 and 119 are drawn to or encompass adenoviral vectors. The application discloses the methods which necessarily require the vectors for successful practice, where said vectors are encompassed by the definitions for **biological material** set forth in 37 C.F.R. § 1.801.

Because it is apparent that these biological materials are essential for practicing the claimed invention, they must be obtainable by a reproducible method set forth in the specification or otherwise be known and readily available to the public as detailed in 37 C.F.R. §§ 1.801 through 1.809.

It is unclear whether this biological material is known and readily available to the public or that the written instructions are sufficient to reproducibly construct this biological material from starting materials known and readily available to the public. Accordingly, availability of such biological material is deemed necessary to satisfy the enablement provisions of 35 U.S.C. § 112. If this biological material is not obtainable or available, the requirements of 35 U.S.C. § 112 may be satisfied by a deposit of the biological material. In order for a deposit to meet all criteria set forth in 37 C.F.R. §§ 1.801-1.809, applicants or assignee must provide assurance of compliance with provisions of 37 C.F.R. §§ 1.801-1.809, in the form of a declaration or applicant's representative must provide a statement. The content of such a declaration or statement is suggested by the enclosed attachment. Because such deposit will not have been made prior to the effective filing date of the instant application, applicant is required to submit a verified statement from a person in a position to corroborate the fact, which states that the biological material which has been deposited is the biological material specifically identified in the application as filed (37 C.F.R. § 1.804). Such a statement need not be verified if the person is an agent or attorney registered to practice before the Office. Applicant is also reminded that the specification must contain reference to the deposit, including deposit (accession) number, date of deposit, name and address of the depository, and the complete taxonomic description.

Response to Arguments

Applicant's arguments have been fully considered but they are not persuasive. Applicant asserts that all vectors and sequences required to produce the claimed vector constructs are identified in the specification. (Remarks, p. 7, ¶¶ 3-4). In addition, Applicant asserts that one of ordinary skill in the art, with the detailed guidance provided can readily construct the vectors of claims 118 and 119.

The claims are directed to a specific vector construct, which is necessarily defined by a unique sequence. Therefore, that intermediate constructs and sequences are readily available does not necessarily equate to reproducibility with respect to the particular construct claimed. In other words, the intermediate components/elements can be used to construct a vector, but if said constructed vector comprises any variance in sequence as compared to the claimed vectors (e.g., a single nucleotide), then said constructed vector would not read on the claimed vectors. For example, different restriction sites can be utilized to mobilize nucleic acids from intermediate constructs into producing the final product.

The specification does not provide sufficient detail so that the allow reproducibility without potential sequence variances. With respect to the Adv_{TET} vector the specification only indicates that the tet-responsive element and transactivator element are built into the opposite ends of the same vector. (e.g., Specification, p. 25, ll. 14-17). No further details are provided as to what specific sequences are mobilized or into what particular restriction sites said sequences are mobilized.

With respect to Ad/FasL-GFP_{TET}, the schematics presented for the intermediate vectors – pLAd-C.tTA and PRAd-T.GFsL – do not provide detailed information.

The specification only indicates that certain sequences are mobilized into an E1 shuttle vector (e.g., Specification, p. 27, ll. 5-10). Further, the disclosure provides generally that a Tet-OFF fusion activator expression cassette is inserted into pLAd-CMVie to generate pLAd-C.tTA and that the GFP-FasL cassette is excised from p10-3.GFsl and inserted into pRAd.mcs to produce pRAd-T.GFsl. (Id.). No details are provided as to specific sequences or restriction site selections. Therefore, the level of detail provided for construction Ad/FasL-GFP_{TET} does not necessarily support the assertion that the same exact construct will be produced time after time (e.g., a single nucleotide variance due to selection of different restriction enzymes used to mobilize intermediate fragments). Moreover, although an intermediate vector or nucleic acid may be currently readily available, there is no assurance that such will be the case for the entire term of an issued patent.

In view of the foregoing, notwithstanding availability of certain intermediate vectors and in light of the general guidance provided in the specification, it must be deemed that the particular vectors, as claimed in claims 118 and 119, would not necessarily be reproducibly constructed. Therefore, the rejection is maintained.

2. **Claims 47, 58-59, 61, 67-69, 71-73 and 115-119 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *in vitro* use of apoptosis-mediated cancer cell death, does not reasonably provide enablement for *in vivo* use.**

This rejection was made in the previous action and is repeated herein. A response to Applicant's arguments is set forth immediately following the body of the rejection.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to *use* the invention commensurate in scope with these claims. All the claims recite "cancer cell" or "tumor" and are directed to destruction of such malignant cells, thus read on gene therapy and *in vivo* use. The test for enablement is whether one skilled in the art could make use the claimed invention from the disclosure in the specification coupled with information known in the art without undue experimentation. *United States v Telectronics Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988). Whether undue experimentation is required is not based upon a single factor but instead is a conclusion reached by weighing many factors which are outlined in *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). The factors include the following:

Scope/Breadth of the claims. The scope/breadth of the claims are broad, where the claims are drawn to a process of inducing cell death *in vivo* in any cancer cell expressing Fas receptor, with an adenoviral vector that encodes FasL.

Nature of the invention. The invention is primarily based on a process involving gene therapy, where a replication-deficient adenoviral vector encoding an apoptosis signaling ligand, such as FasL, is used to transfect cells, with subsequent regulated expression (e.g. via the Tet-responsive regulatory element or tissue-specific promoters) of the ligand in cells that may express the Fas receptor. Put another way, the Fas/FasL apoptosis pathway is directed toward inducing death in cancer cells. The claims read on *in vivo* use, i.e., eradication of cancerous cells or tumors, including in any subject (e.g. immunocompetent patient).

State of the art/ Unpredictability of the art. The invention is directed to *in vivo* gene therapy and specifically to targeting tumor cells expressing Fas receptor using an adenoviral expression construct encoding FasL. With regard to gene therapy, the state of art is also poorly developed. "...there is still no conclusive evidence that gene-therapy protocol has been successful in the treatment of a human disease." (*See*, Anderson, Nature, 1998; 392: 25-30, at 25). Gene therapy is still a highly unpredictable art within biology and medicine. For example, nucleic acids encoding therapeutic products may be erroneously inserted, thus disrupting a particular gene resulting in unknown, adverse or detrimental effects. (*See*, Check, E., Nature, 2003;421: 678) (citing occurrence of leukemia due to insertion nucleic acids used in gene therapy into a particular stretch of DNA); (*See also*, Juengst, ET. BMJ, 2003;326:1410-11;indicating that gene transfer often has multiple and unpredictable effects on cells).

In addition, with regard to adenoviral vectors for targeting tumor targeting *in vivo*, there is a substantial risk of vector immunogenicity, such as localized inflammation that can occur at the site of gene transfer due to T- or B-Cell mediated targeting of transduced cells. In addition, both neutralizing (which would hinder expression of the therapeutic gene; i.e. FasL) and non-neutralizing anti-adenovirus antibodies are capable of activating complement. (*See supra*, Green and Seymour, at 1039, col. 2, ¶ 2).

Furthermore, with regard to use of adenoviral vectors in tumor targeting, there are significant hurdles that need to be overcome: infection of or transfer to non-target cells, evasion of neutralization by anti-adenoviral antibodies, viral interaction with blood cells, immune parameters affecting efficacy and toxicity and viral bio-distribution. (*See*, Green and Seymour. Cancer Gene Therapy; 2002;9:1036-42, pp. 1039-40).

In addition, while the Fas and FasL mediated pathway for apoptosis is well characterized, studies conducted with regard to targeted inducement of cell death have been exclusively *in vitro* or in immunocompromised mice. (e.g., Arai et al. *Gene transfer of Fas ligand induces tumor regression in vivo*. Proc. Natl. Acad. Sci. Dec. 1997; 94:13862-7; showing apoptosis of renal and colon carcinoma tumors implanted into flanks of nude mice, where tumors were injected with adenoviral vectors expressing FasL). More importantly, clinical studies studying the therapeutic effect of FasL in killing cancer cells were disappointing due to "severe toxicity observed in preclinical studies". (*See*, Rossi and Gaidano. Haematologica/J. Hematology, 2003; 88(2):212-18, at 217).

Moreover, Fas receptors are widely expressed by many non-cancerous cells in the body, therefore extending the potential for toxicity to different tissue/organs. Therefore, FasL expression could have deleterious effects on normal cells expressing Fas receptor (e.g. hepatocytes). This can occur whether transfected cancer cells express with subsequent systemic delivery to non-target sites or whether non-target cells are transduced and express FasL. In regard to hepatotoxicity, because there are a substantial number of Fas receptors expressed in liver cells, such cells/tissue would be susceptible to FasL mediated apoptosis. Notwithstanding regulated FasL expression, *in vitro* results do not necessarily translate into *in vivo* use. For example, having even a base line level of FasL expression or "leaky" expression can result in unintended toxic effects, making practice of invention unpredictable. Furthermore, if viral vectors enter the systemic system, they can be delivered to other cells exacerbating the host's immune response.

Therefore, it would follow that there is a great deal of unpredictability as to whether expression of FasL *in vivo* would result in cell death in cancer cells expressing Fas receptor. In sum, the state of art, with respect to *in vivo* expression of a ligand in a ligand-receptor mediated (e.g. Fas-FasL) apoptosis, is still developing with many substantial concerns and question yet to be resolved.

In addition, expressing FasL may have unintended deleterious effects on the subject's anti-cancer defense. One such effect is tumor immune privilege; this occurs where intra-tumoral lymphocytes, such as natural killer cells (the main anti-tumor effector cells, which highly express Fas receptor) are actually "attacked" by cancer cells that express FasL. (*See*, O'Connell et al. Nature Med., 1999;5(3):267-8, at 267). This is relevant to the instant invention because in regard to the claimed embodiments, the FasL expressed could in effect "attack" the natural killer cells, i.e., non-target cells, thus injecting further unpredictability with respect to *in vivo* practice of the claimed invention. Of course, safety and efficacy are not enablement requirements, but certainly are factors that exacerbate unpredictability with regard to practicing the invention.

In sum, it must be deemed that there is a great deal of unpredictability that is attendant with practicing the claimed invention *in vivo*.

Amount of guidance provided/working examples. The specification provides a single example replication-deficient adenoviral vector expressing a murine FasL (i.e. rAD/FasL-GFP_{TETd}) that results in apoptosis of cells expressing the Fas receptor, *in vitro* cell culture and *in vivo* in immunocompromised mice, where breast cancer and prostate cancer cell lines are deposited in nude mice.

In addition the disclosure indicates experiments involving immunocompetent dogs were conducted, but there are no results set forth. (Spec. pp. 39-40, "Toxicology...beagles"). The examples do not provide any significant guidance with respect to unpredictability in practicing the claimed invention in *in vivo* in an immunocompetent subject. For example, there is no significant guidance provided with respect to circumventing obstacles such as immunotoxicity and immunoneutralization that would be attendant with *in vivo* application in human subjects. Furthermore, there is no relevant or significant guidance provided with respect to obstacles and unpredictability in regard to FasL expression in non-target cells, for example. Moreover, no other combinations of receptor/ligand are taught in the instant specification, *in vivo* or otherwise.

Amount of experimentation required. The level of skill in the art required to practice the claimed invention is high. Given the unsolved hurdles to successfully practicing the invention, the level of unpredictability in the art and lack of working examples *in vivo* with immunocompetent subjects, as outlined above, it must be considered that the skilled artisan would be required to conduct trial and error experimentation of an undue, unpredictable nature in order to attempt to practice the claimed invention commensurate with claims' scope. Applicant should note that obstacles and hurdles to successful practice may inhere safety and efficacy concerns, but nonetheless are relevant, only in so far as they prevent one of skill to *use* the invention commensurate with the scope of the claims.

Response to Arguments

Applicant's arguments in regard to obviating the enablement rejection are not deemed persuasive.

Applicant asserts that a tissue specific or inducible promoter allows regulated expression with efficient delivery to target cells and more uniform regulation of FasL expression. (Remarks, p. 10, ¶ 1; p. 11, first full ¶; p. 12, first full ¶). Second, Applicant asserts that *in vivo* applications are enabled and supported because the specification teaches that 14 mice were administered Ad/FasL-GFP$_{TET}$ without lethality and with tumor regression. (Remarks, p. 10, ¶ 2). Third, Applicant asserts that the disclosure exceeds the standard because the issues of unpredictability are limited to safety and efficacy concerns of practicing the invention. (Remarks, p. 13, ¶ 1).

The scope of the claims must bear a reasonable correlation with the scope of the enablement as provided in the specification. (*In re Fisher*, 166 USPQ 19, 24 (CCPA 1970)). The instant disclosure does not provide a sufficient enabling disclosure commensurate to the full scope of the claims. As to cell specific or inducible promoters, the utilization of such promoters does not address predictability with respect to target delivery (i.e., efficient delivery to target cells) and sufficient expression levels, obstacles that are attendant to any gene therapy protocol for *in vivo* delivery of therapeutic proteins. In other words, whether the expression is constitutive or cell-specific or inducible, the issue of target delivery *in vivo* would remain of equal concern. Therefore, having a relatively higher level of regulation (e.g., CMV versus hepatic-specific promoter elements) is of little moment where unpredictability is grounded in lack of sufficient delivery and transient expression levels.

Furthermore, whether inducible or tissue-specific, the FasL protein may be expressed in non-target or non-cancerous cells, with implications of immunotoxicity. In other words, a higher level of regulation of a toxic protein does little to obviate the unpredictability with respect to expression of an exogenous protein *in vivo* in an immunocompetent host.

In addition, inducible or specific promoters do little to address unpredictability with respect to neutralization by anti-adenoviral antibodies, as well as immune parameters affecting efficacy, toxicity and viral bio-distribution. Again, the issue is one of delivery and not regulated expression of a protein. Moreover, where the teachings in the art are conflicting (e.g., in regard to immune toxicity), the conflict in essences defines unpredictability, i.e., results can vary.

Applicant asserts that vectors may be infused intravenously or injected directly into an organism. (Remarks, p. 11, first full ¶). In particular, Applicant notes that Arai et al. teaches that "direct injection into the subcutaneous tumor mass appears to be localized and does not give rise to [toxicity, such as fulminant hepatitis]..." (e.g., p. 13864, last sentence of ¶ 1). However, the very same cited paragraph teaches that inflammation is observed in the abdominal muscle layer beneath the injection point in Adv-FasL treated mice and that intravenous (i.e., infusion) result in fulminant hepatitis. (e.g., p. 13864, ¶ 1, bottom half).

Applicant asserts that in considering tumor immune privilege, the vectors (i.e., FasL expression) are localized in cancer cells comprising the tumor, thus any immune cell death is also localized without systemic repercussions. However, the claims are directed to administration (i.e., transduction) through any mechanism. It follows that with respect to tumor immune privilege, the delivery of viral vectors and therefore FasL expression is not limited to a particular locus. Arguendo, if the mode of administration is through direct injection into tumor, there remains unpredictability in regard to immunotoxicity (e.g., inflammation).

In regard to Applicant's second argument, Applicant submits Exhibit A (FasL-mediated death of human breast cancer cells transplanted in nude mice), as evidence that one of skill could use the invention *in vivo*.

However, as noted in actions of record and herein, an immunocompetent model would not address concerns such as immunotoxicity or immunoneutralization (e.g., in regard to adenoviral vectors), which in turn present obstacles to successful practice of the claimed invention. Furthermore, an immunocompromised model system would not address obstacles presented such as the unpredictability of FasL expression in non-target cells (e.g., hepatocytes) or delivery of FasL to unintended cells/tissue. Lastly, issues having to do with safety or efficacy are relevant to an enablement analysis insofar as such issues are relevant to unpredictability. In sum, Applicant's argument is primarily based on the assertion that specific or inducible promoter elements obviate any concerns of unpredictability with respect to gene therapy to induce cancer cell death *in vivo*. However, expression regulation does not address unpredictability with respect to viral delivery in the context of gene therapy and immunotoxicity in an immunocompetent organism. The prior art teaches that there are obstacles that make *in vivo* application unpredictable as stated in the foregoing. Further, issues of safety/efficacy are germane to assessing the level of unpredictability for *in vivo* processes. In view of the above stated reasons, the enablement rejection is maintained.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action.

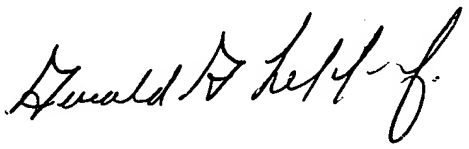
In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ray Akhavan whose telephone number is 571-272-0766. The examiner can normally be reached between 8:30-5:00, Monday-Friday. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, PhD, can be reached on 571-272-0781. The fax phone numbers for the organization where this application or proceeding is assigned are 571-273-8300 for regular communications and 703-872-9307 for After Final communications.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully submitted,

Ray Akhavan/AU 1636



GERRY LEFFERS
PRIMARY EXAMINER